

BH

(12) UK Patent Application (19) GB (11) 2 060 622 A

(21) Application No 8028715

(22) Date of filing 5 Sep 1980

(30) Priority data

(31) 7932046

(32) 14 Sep 1979

(33) United Kingdom (GB)

(43) Application published
7 May 1981

(51) INT CL³
C07C 121/75
A61K 31/135
C07C 147/00
C07D 213/63 215/20
241/18 277/34 333/32

(52) Domestic classification
C2C 1382 1510 1530
1534 1620 213 215 220
226 227 22Y 250 251 252
254 256 25Y 29X 29Y
30Y 322 323 326 32Y 364
36Y 396 397 500 50Y 613
620 624 650 672 682 699
802 80Y AA LF LY RN

(56) Documents cited
GB 1493961
JP 7700941
J. Pharmacol Exp Ther 193
804—11 (1975)
J. Pharm Soc Japan 93
508—19 (1973)

(58) Field of search
C2C

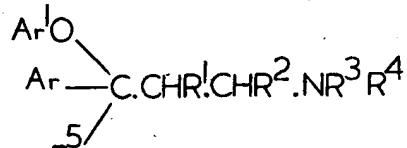
(71) Applicant
John Wyeth & Brother
Limited,
Huntercombe Lane South,
Taplow, Maidenhead,
Berkshire, England

(72) Inventor
Robin Gerald Shepherd

(74) Agent
K. J. S Brown,
Wyeth Laboratories,
Huntercombe Lane South,
Taplow, Maidenhead,
Berkshire, England

(54) 3-Aryl-3-aryloxyalkylamines

(57) 3-Aryl-3-aryloxyalkylamines of
the general formula (I)



and their pharmaceutically acceptable
acid addition salts, wherein R¹, R², R⁴

and R⁵ are hydrogen or lower alkyl, R³
is hydrogen, lower alkyl or benzyl, Ar¹
is phenyl optionally substituted by one
or more halogen, trifluoromethyl,
lower alkyl, lower alkoxy, nitro or
amino groups, and Ar¹ is
methylsulphonyl, methylsulphonyl- or
cyano-substituted phenyl, 2- or 4-
pyridyl, 2-pyrazinyl, 2-quinolinyl, 2-
thienyl or 2-thiazolyl exhibit activity on
the central nervous system, e.g. as
antidepressants.

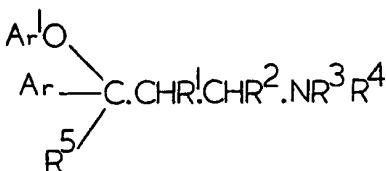
Certain of the chemical formulae
appearing in the printed
specification were submitted in
formal form after the date of
filing.

GB 2 060 622 A

SPECIFICATION
3-Aryl-3-aryloxypropylamines

This invention relates to 3-aryl-3-aryloxypropylamines, to a process for preparing them, to their use and to pharmaceutical preparations containing them.

5 The present invention provides 3-aryl-3-aryloxypropylamines of the general formula (I)



and their pharmaceutically acceptable acid addition salts, wherein R¹, R², R⁴ and R⁵ are hydrogen or lower alkyl, R³ is hydrogen, lower alkyl or benzyl, Ar is phenyl optionally substituted by one or more halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro or amino groups and Ar¹ is methylsulphonyl-, 10 methylsulphonyl- or cyano-substituted phenyl, 2- or 4-pyridyl, 2-pyrazinyl, 2-quinolinyl, 2-thienyl or 2-thiazolyl.

The invention also provides process for preparing a compound of general formula (II) or a pharmaceutically acceptable acid addition salt thereof, which comprises reacting an anion of an alcohol of general formula (III)



15

(where Ar, R¹, R², R³, R⁴ and R⁵ are as defined above) with a halo compound of general formula (III)



[where X is fluorine and Ar¹ is a methylsulphonyl-, methyl-sulphonyl- or cyano-substituted phenyl radical or X is fluorine, chlorine or bromine (preferably fluorine) and Ar¹ is 2- or 4-pyridyl, 2-pyrazinyl, 2-quinolinyl, 2-thienyl or 2-thiazolyl. The reaction may be carried out in a dipolar aprotic solvent. Examples of dipolar aprotic solvents include dimethylsulphoxide, dimethylformamide, hexamethylphosphoric triamide and sulpholane. Preferably the solvent is dimethylsulphoxide. The anion of the alcohol of general formula (II) is preferably formed by reacting the alcohol with potassium or sodium hydride or an alkyl or phenyl lithium (e.g. butyl lithium) in a compatible dipolar aprotic solvent. Preferably the alcohol is reacted with sodium hydride.]

20 25 The process of the invention can be carried out at convenient temperatures e.g. 0 to 100°C (for example room temperature); there is generally no need to use reflux temperatures. Good yields of products are generally obtained in relatively short reaction times (e.g. within two to three hours).

If in the process described above the compound of the general formula (II) is obtained as an acid 30 addition salt, such as a pharmaceutically acceptable acid addition salt or an acid addition salt such as an oxalate, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base a pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with the conventional procedures for preparing acid addition salts from base

35 compounds.]

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric acetic, formic, methanesulphonic and p-toluenesulphonic acids.

Once a compound of general formula (I) is obtained, if desired it can be converted into another 40 compound of general formula (II) methods. For example, a 3-aryl-3-aryloxypropylamine of formula (I) in which R³ and R⁴ are methyl can be converted to the compound in which one group is methyl and the other hydrogen by treatment with cyanogen bromide or ethyl or phenyl chloroformate followed by basic hydrolysis.

The compounds of general formula (I) possess one or more asymmetric carbon atoms, depending 45 upon the particular substituents. The compounds can therefore exist in various stereochemical forms. It will be realised that if the starting material of formula (II) is a mixture of isomers the product of formula (II) will also be a mixture of isomers which may be separated, if required, by standard procedures. If the starting material is a single isomer then the product will also be a single isomer.

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms.

The radical preferably contains 1 to 4 carbon atoms. Examples of lower alkyl radicals include methyl, ethyl, propyl and butyl. Examples of lower alkoxy radicals include methoxy, ethoxy, propoxy and butoxy. Examples of lower alkenyl radicals include allyl and methallyl. When R¹, R² and/or R³ represent lower alkyl, the lower alkyl group is preferably a straight chain radical such as methyl, ethyl, n-propyl or n-butyl although R³ may also be, for example, a branched chain lower alkyl group such as isopropyl. R¹, R² and R⁵ are preferably hydrogen.

The compounds of general formula (I) and their pharmaceutically acceptable acid addition salts, including the novel compounds of the invention, generally possess pharmacological activity. In particular the compounds exhibit activity on the central nervous system, e.g. as antidepressants, as indicated by one or more of the standard pharmacological test procedures such as the reserpine hypothermia procedure based upon B. M. Askew, Life Sciences (1963), 1,725—730, the inhibition of noradrenaline or 5-hydroxytryptamine uptake in rat brain slices, the potentiation and prolongation of the effects of amphetamine and the modification of the effects of p-chloroamphetamine. For example, N-methyl-3-(2-pyridyloxy)-3-phenylpropylamine, a representative compound of the invention, in the reserpine hypothermia procedure produced a rise in rectal temperature compared to the control of 8.7°C at 10 mg/kg and 10.7°C at 30 mg/kg.

The invention further provides a method of treating depression which comprises administering to a warm blooded mammal animal, particularly a human, a therapeutically effective amount of a compound of the invention. The invention also provides a pharmaceutical composition comprising a compound of the invention in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 5 mg. or less to 500 mg. or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of the carrier where the compounds are in unit dosage form.

The following Examples illustrate the invention.

55 Example 1

3-(4-Cyanophenoxy)-N,N-dimethyl-3-phenylpropylamine

A mixture of N,N-dimethyl-3-hydroxy-3-phenylpropylamine (3.58 g, 20 mM), 50% sodium hydride dispersion (1 g) and DMSO (50 ml) was heated at 80° until homogeneous, cooled to ambient temperature and treated dropwise with a solution of 4-fluorobenzonitrile (2.42 g, 20 mM) in DMSO with cooling (exothermic). After 1 h the reaction mixture was poured on to water (200 ml) and extracted with ether (2×200 ml). The ether extract was extracted with 1N hydrochloric acid (2×50 ml), the acid extract basified and then extracted with ether (2×200 ml). The ether was dried and the solvents removed under reduced pressure to give an oil which was dissolved in ethyl acetate and treated with an excess of a solution of oxalic acid dihydrate in ethyl acetate. Removal of the resultant precipitate by

filtration followed by recrystallisation from ethyl acetate gave the title compound (4.8 g) as the oxalate quarter hydrate m.p. 80° (decomp).

Found: C, 64.1; H, 6.05; N, 7.7%
 $C_{18}H_{20}N_2O \cdot C_2H_2O_4$ requires: C, 64.1; H, 6.1; N 7.5%

5 Example 2

3-(4-Cyanophenoxy)-N-methyl-3-phenylpropylamine

A mixture of 3-hydroxy-N-methyl-3-phenylpropylamine (2.5 g, 15 mM), 50% sodium hydride dispersion (750mg) and DMSO (50 ml) were heated at 80° until homogeneous, cooled to ambient temperature and treated with a solution of 4-fluorobenzonitrile (1.82 g, 15 mM) in DMSO (10 ml).

10 After 1 h the mixture was poured on to water (250 ml) and extracted with ether (2×250 ml). The combined ether layers were extracted with 2N hydrochloric acid (2×25 ml), the acid extracts basified and extracted with ether (2×100 ml). The organic phase was dried, evaporated and the residue dissolved in ethyl acetate. Treatment with an excess of a solution of oxalic acid in ethyl acetate gave the title compound as the oxalate (3 g) m.p. 131—3°.

15

Found: C, 64.0; H, 5.9; N 8.0%
 $C_{17}H_{18}N_2O \cdot C_2H_2O_4$ requires: C, 64.0; H, 5.7; N, 7.9%.

15

Example 3

N,N-Dimethyl-3-(2-pyridyloxy)-3-phenylpropylamine

A mixture of N,N-dimethyl-3-hydroxy-3-phenylpropylamine (4.48 g, 25 mM), prewashed 50% sodium hydride (1.25 g, 25 mM) and DMSO (50 ml) was maintained at 80° until homogenous, cooled to ambient temperature and treated with a solution of 2-fluoropyridine (2.72 g, 25 mM) in DMSO (10 ml). After 1 h the mixture was poured on to water (250 ml) and extracted with ether (2×250 ml). The combined organic extracts were washed with brine, dried and evaporated. The residue was dissolved in ethyl acetate and added to an excess of a solution of oxalic acid dihydrate in ethyl acetate. Removal of the resulting precipitate by filtration followed by drying in vacuo gave the title compound as the oxalate quarter hydrate (5.8 g) m.p. 133—5°.

25 Found: C, 61.6; H, 6.5; N, 7.8%
 $C_{18}H_{22}N_2O_5 \cdot \frac{1}{2}H_2O$ requires: C, 61.6; H, 6.5; N, 8.0%.

Example 4

N-Methyl-3-(2-pyridyloxy)-3-phenylpropylamine

A mixture of 3-hydroxy-N-methyl-3-phenylpropylamine (4.1 g, 25 mM), prewashed 50% sodium hydride (1.25 g, 25 mM) and DMSO (50 ml) was obtained at 80° until homogeneous, cooled to ambient temperature and treated with a solution of 2-fluoropyridine (2.72 g, 25 mM) in DMSO (10 ml). After 1 h the mixture was poured on to water (250 ml) and extracted with ether (2×250 ml). The combined organic extracts were washed with brine, dried and evaporated. The residue was dissolved in ethyl acetate and added to an excess of a solution of oxalic acid in ethyl acetate. The resultant precipitate was removed by filtration and dried in vacuo to give the title compound as the oxalate (5.5 g) m.p. 161—3° (decomp.).

30 Found: C, 61.1; H, 6.2; N, 8.3%
40 $C_{15}H_{18}N_2O \cdot C_2H_2O_4$ requires: C, 61.4; H, 6.1; N, 8.4%.

30

35

45

50

Example 5

N,N-Dimethyl-3-(4-methylsulphinylphenoxy)-3-phenylpropylamine

A mixture of N,N-dimethyl-3-hydroxy-3-phenylpropylamine (3.58 g, 20 mM), 50% sodium hydride dispersion (1 g) and DMSO (50 ml) was heated at 80° until homogeneous, cooled to room temperature and treated dropwise with a solution of 1-fluoro-4-methylsulphinylbenzene (3.16 g, 20 mM) in DMSO (10 ml) (slightly exothermic). After 2 hours the reaction mixture was poured onto water (200 ml) and extracted with ether (2×200 ml). The ether layer was extracted with 1N hydrochloric acid (2×50 ml), the extracts basified, extracted with ether (2×200 ml). The final ether extracts were dried, and the solvent removed under reduced pressure to give an oil which was taken up in ethyl acetate (250 ml). Removal of the resultant precipitate by filtration and drying in vacuo gave the title compound as the oxalate hemihydrate (6.3 g), m.p. 110—112°.

Found: C, 57.75; H, 6.45; N, 3.2%
 $C_{18}H_{23}NO_2S \cdot C_2H_2O_4 \cdot \frac{1}{2}H_2O$ required: C, 57.7; H, 6.3; N, 3.4%.

Example 6**N,N-Dimethyl-3-(4-methylsulphonylphenoxy)-3-phenylpropylamine**

A mixture of N,N-dimethyl-3-hydroxy-3-phenylpropylamine (3.58 g, 20 mM) 50% sodium hydride dispersion (1 g) and DMSO (50 ml) was heated at 80° until homogenous, cooled to ambient

5 temperature and treated dropwise with a solution of 1-fluoro-4-methylsulphonylbenzene (3.48 g, 20 mM) in DMSO (10 ml) (slightly exothermic). After 1 hour the reaction mixture was poured onto water (200 ml) and extracted with ether (2 x 200 ml). The ether extract was extracted with 1N hydrochloric acid (2 x 50 ml), the acid layer basified and extracted with ether (2 x 200 ml). The ether layer was dried, the solvents removed under reduced pressure, the residue dissolved in ethyl acetate and treated with
10 an excess of a solution of oxalic acid in ethyl acetate. Removal of the resultant precipitate by filtration followed by recrystallisation from acetone gave the title compound as the oxalate (4.5 g), m.p. 182—4°.

Found: C, 56.9; H, 6.25; N, 3.3%
 $C_{18}H_{23}NO_3S \cdot C_2H_2O_4$ requires: C, 56.7; H, 6.0; N, 3.3%.

15 Example 7**N,N-Dimethyl-3-phenyl-3-(2-pyrazinylloxy)propylamine**

Following the method of Example 3, reaction of N,N-dimethyl-3-hydroxy-3-phenylpropylamine, sodium hydride and 2-chloropyrazine in DMSO gives the title compound.

Example 8**20 N-Methyl-3-phenyl-3-(2-quinolylloxy)propylamine**

Following the method of Example 4, reaction of 3-hydroxy-N-methyl-3-phenylpropylamine, sodium hydride and 2-chloroquinoline in DMSO gives the title compound.

Example 9**N,N-Dimethyl-3-phenyl-3-(2-thiazolylloxy)propylamine**

25 Following the method of Example 3, reaction of N,N-dimethyl-3-hydroxy-3-phenylpropylamine, sodium hydride and 2-bromothiazole in DMSO gives the title compound.

Example 10**N-Methyl-3-phenyl-3-(2-thienylloxy)propylamine**

30 Following the method of Example 4, reaction of 3-hydroxy-N-methyl-3-phenylpropylamine, sodium hydride and 2-fluorothiophen in DMSO gives the title compound.

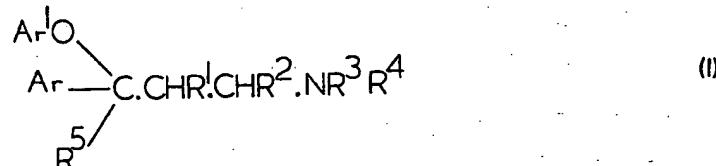
Example 11**N,N-Dimethyl-3-(4-pyridyloxy)-3-phenylpropylamine**

A solution of the sodium salt of N,N-dimethyl-3-hydroxy-3-phenylpropylamine in DMSO is generated as in Example 3 then treated with a solution of 4-chloropyridine in ether (generated by
35 dissolving 4-chloropyridine hydrochloride in water, adjusting the pH to 8.5 with sodium bicarbonate, extracting the aqueous solution with toluene, evaporating the toluene under reduced pressure and dissolving the residue in ether).

Aqueous work up of the reaction mixture as in Example 3 gives the title compound.

Claims

40 1. A 3-aryl-3-aryloxypropylamine of the general formula 40



or a pharmaceutically acceptable acid addition salt thereof wherein R¹, R², R⁴ and R⁵ are hydrogen or lower alkyl, R³ is hydrogen, lower alkyl or benzyl, Ar is phenyl optionally substituted by one or more halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro or amino groups, and Ar¹ is methylsulphonyl-, methylsulphonyl- or cyano-substituted phenyl, 2- or 4-pyridyl, 2-pyrazinyl, 2-quinolyl, 2-thienyl, or 2-thiazolyl.

45 2. A compound as claimed in Claim 1 wherein R⁵ is hydrogen.

3. A compound as claimed in Claim 1 or 2 wherein R¹ and R² are both hydrogen.

4. A compound as claimed in any one of the preceding claims wherein Ar is phenyl.

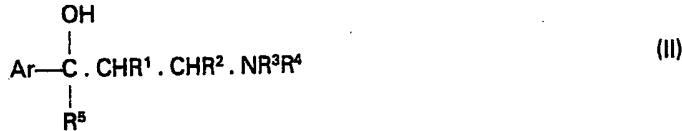
50 5. 3-(4-Cyanophenoxy)-N,N-dimethyl-3-phenylpropylamine or a pharmaceutically acceptable acid addition salt thereof.

6. 3-(4-Cyanophenoxy)-N-methyl-3-phenylpropylamine or a pharmaceutically acceptable acid addition salt thereof.

7. N,N-Dimethyl-3-(2-pyridyloxy)-3-phenylpropylamine or a pharmaceutically acceptable acid addition salt thereof.

8. N-Methyl-3-(2-pyridyloxy)-3-phenylpropylamine or a pharmaceutically acceptable acid addition salt thereof.

5 9. A process for preparing a compound claimed in Claim 1 which comprises reacting an anion of an alcohol of general formula (II). 5



(where Ar, R¹, R², R³, R⁴ and R⁵ are as defined in Claim 1) with a halo compound of general formula (III)



10 10. (where X is fluorine and Ar¹ is methylsulphonyl-, methylsulphonyl- or cyano-substituted phenyl radical 10 or X is fluorine, chlorine or bromine and Ar¹ is 2- or 4-pyridyl, 2-pyrazinyl, 2-quinolinyl, 2-thienyl or 2-thiazolyl) and, if desired converting a free base of general formula (I) into a pharmaceutically acceptable acid addition salt thereof.

10. A process as claimed in Claim 9 wherein the anion of the alcohol of general formula (II) is 15 formed by reacting the alcohol with potassium or sodium hydride or with an alkyl or phenyl lithium. 15

11. A process for preparing a compound claimed in claim 1 substantially as hereinbefore described with reference to any one of the Examples.

12. A compound as claimed in Claim 1 whenever prepared by the process claimed in any one of Claims 9 to 12.

20 13. A pharmaceutical composition comprising a compound claimed in any one of Claims 1 to 8 and 12 in association with a pharmaceutically acceptable carrier.

14. A compound claimed in any one of Claims 1 to 8 and 12 for use as an antidepressant.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981. Published by the Patent Office,
25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/022313

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0101973	A	11-01-2001	AU 771258 B2 AU 5633700 A BR 0012136 A CA 2375908 A1 CN 1379672 T CZ 20014625 A3 EP 1196172 A2 EP 1459748 A1 EP 1459749 A1 EP 1459750 A1 EP 1459751 A1 HU 0201623 A2 JP 2003503450 T MX PA02000562 A NO 20016406 A NZ 515885 A PL 352252 A1 SK 19382001 A3 WO 0101973 A2 US 2002061910 A1 US 2002086864 A1 US 2002107249 A1 US 2002128173 A1 US 2003040464 A1 US 6465458 B1 US 2004058925 A1 US 2004147614 A1 ZA 200110325 A	18-03-2004 22-01-2001 11-06-2002 11-01-2001 13-11-2002 14-08-2002 17-04-2002 22-09-2004 22-09-2004 22-09-2004 22-09-2004 28-09-2002 28-01-2003 02-07-2002 19-02-2002 27-08-2004 11-08-2003 02-07-2002 11-01-2001 23-05-2002 04-07-2002 08-08-2002 12-09-2002 27-02-2003 15-10-2002 25-03-2004 29-07-2004 14-03-2003
WO 9915177	A	01-04-1999	AU 9214498 A CA 2304112 A1 EP 0909561 A2 JP 2001517628 T WO 9915177 A1 US 6046193 A	12-04-1999 01-04-1999 21-04-1999 09-10-2001 01-04-1999 04-04-2000
GB 2167407	A	29-05-1986	DE 3540093 A1 FR 2573425 A1 IT 1190420 B JP 6067916 B JP 61129174 A	28-05-1986 23-05-1986 16-02-1988 31-08-1994 17-06-1986
WO 0039091	A	06-07-2000	AT 266637 T AU 760874 B2 AU 1290500 A BG 105731 A BR 9916680 A CA 2350589 A1 CN 1332727 T CZ 20012388 A3 DE 69917327 D1 DK 1140835 T3 EE 200100347 A EP 1140835 A1 HR 20010491 A1 HU 0105075 A2 WO 0039091 A1 ID 29052 A	15-05-2004 22-05-2003 31-07-2000 28-02-2002 13-11-2001 06-07-2000 23-01-2002 11-09-2002 17-06-2004 09-08-2004 16-12-2002 10-10-2001 31-08-2002 29-04-2002 06-07-2000 26-07-2001

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D413/12 A61K31/5377 A61P25/00 A61P25/18

CA

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/01973 A (MARSHALL ROBERT CLYDE ; UPJOHN CO (US); WONG ERIK H F (US); BIRGERSON) 11 January 2001 (2001-01-11) cited in the application claims 1,13-38	1,13-18
A	WO 99/15177 A (HEILIGENSTEIN JOHN HARRISON; LILLY CO ELI (US)) 1 April 1999 (1999-04-01) cited in the application the whole document	1,13-18
A	GB 2 167 407 A (ERBA FARMITALIA) 29 May 1986 (1986-05-29) claims 1,14-17	1,13,14, 16

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

29 October 2004

Date of mailing of the international search report

08/11/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Hass, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/39091 A (SEGELSTEIN BARBARA EILEEN; LIRAS SPIROS (US); PFIZER PROD INC (US); A) 6 July 2000 (2000-07-06) claims 1,14-36	1,13,14
A	THORNBER C W: "ISOSTERISM AND MOLECULAR MODIFICATION IN DRUG DESIGN" CHEMICAL SOCIETY REVIEWS, CHEMICAL SOCIETY, LONDON, GB, vol. 8, no. 4, 1979, pages 563-580, XP001105105 ISSN: 0306-0012 page 564, table 1	
A,P	WO 2004/017977 A (CLARK BARRY PETER ; HAUGHTON HELEN LOUISE (GB); WALTER MAGNUS WILHELM) 4 March 2004 (2004-03-04) claims	1,5, 13-18
A,P	WO 2004/018440 A (CLARK BARRY PETER ; HAUGHTON HELEN LOUISE (GB); GALLAGHER PETER THADDE) 4 March 2004 (2004-03-04) claims	1,5, 13-18
A,P	WO 03/106441 A (AIROLDI ANNALISA ; MARTINI ALESSANDRO (IT); PHARMACIA ITALIA SPA (IT);) 24 December 2003 (2003-12-24) claims 1-9	1,13-18